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Consistencies and Inconsistencies Underlying the Quantitative Assessment of Leukemia Risk from Benzene Exposure

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This paper examines recent risk assessments for benzene and observes a number of inconsistencies within the study and consistencies between studies that should effect the quantitative determination of the risk from benzene exposure. Comparisons across studies show that only acute myeloid leukemia (AML) is found to be consistently in excess with significant benzene exposure. The data from the Pliofilm study that forms the basis of most quantitative assessments reveal that all the AML cases came from only one of the three studied plants and that all the benzene exposure data came from the other plants. Hematological data from the 1940s from the plant from which almost all of the industrial hygiene exposure data come do not correlate well with the originally published exposure estimates but do correlate well with an alternative set of exposure estimates that are much greater than those estimates originally published. Temporal relationships within the study are not consistent with those of other studies. The dose-response relationship is strongly nonlinear. Other data suggest that the leukemogenic effect of benzene is nonlinear and may derive from a threshold toxicity.

Introduction

Quantitative assessments of the carcinogenic (leukemogenic) risk from benzene exposure have been of regulatory importance since the U.S. Supreme Court (*1*) in 1980 overturned the 1978 OSHA (Occupational Safety and Health Administration, US) benzene standard, primarily because OSHA did not demonstrate that a significant risk of leukemia existed under the previous benzene standard. Quantitative risk assessment has subsequently become the standard method used by regulatory agencies to estimate the cancer risk under a specific exposure scenario. The process of quantitative risk assessment attempts to discover underlying uniformity and continuity among numerous studies that each reflect different aspects of the risk relation between exposure and disease—each with its own deviance from the "truth." The sources and magnitude of these deviances, while often unclear, can be shown and assessed more clearly by asking similar critical questions of each study to define clearly the underlying assumptions and by testing those underlying assumptions. This paper deals with the concept of consistency among the studies that generally support the concept of an association between benzene exposure and excess risk of leukemia and within the studies critical to the quantitative assessment of that risk. Although the largest studies relating benzene and cases of leukemia are those of Aksoy (*2*) in Turkey (51 cases), Vigliani (*3*) in Italy (24 cases), and Yin (*4*) in China (30 cases), the largest United States study (9 cases) which was conducted by the National Institute for Occupational Safety and Health (NIOSH) (*5*) serves as the primary basis for the quantitative assessment of leukemia risk from benzene exposure. The findings of the larger studies are compared with the NIOSH study for consistency of findings across studies, and the NIOSH study is examined in detail later in this paper for consistency within the study.

The basic classification of leukemias is reviewed as a prelude to a review of the types of leukemia noted in studies of benzene exposed workers. The critical NIOSH study (*6*) is then reviewed with respect to the relationship between the leukemia cases and the benzene exposure data presented in the paper. Finally, this paper considers some of the consequences of these observations on the

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theoretical shape of the dose-response curve between benzene and leukemia.

Observations from the Literature on Benzene and Leukemia

Classification of Lymphomas and Leukemias

In the International Classification of Diseases (ICD-9-ICM) (*6*), leukemias fit in the general class called Neoplasms of the Lymphopoietic and Hematopoietic Tissues (ICD numbers 200 to 208) as seen in Table 1. The basic hematopoietic tissues, found in the bone marrow, are the precursors of blood cells. One primary cell line is the lymphoid line of cells, which originates in areas such as the lymph nodes and forms cancers such as lymphomas (solid tumors), multiple myelomas (cancer of the plasma cell), and lymphoid leukemias, often with invasion of free cells in the blood or proliferating in the bone marrow. A second line, the myeloid line (from myelos, meaning marrow) forms the leukemias known as myelogenous (meaning originating from the marrow cells) or as granulocytic (since their cytoplasm shows granules when fixed and stained).

Within the classification of leukemia, lymphocytic leukemias derive from lymphoid or lymphopoietic tissue; myelocytic (and monocytic) leukemias derive from myeloid or hematopoietic tissue. Each cell type further differentiates into two different types of leukemia based on whether the dominant cell is immature (acute) or mature (chronic). Thus, the four major types of leukemia are acute lymphoid leukemia (ALL), chronic lymphoid leukemia (CLL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML).

The ICD numbers (Table 1) reflect distinctions that can generally be made both in a medical diagnosis and in differences in development of the cell types. These leukemias also differ in characteristics of the age of the patients, their causes, their clinical patterns, and their response to different therapeutic interventions. Each type has a number of variants. The acute myeloid leukemias (AML) can be further subclassified (*7*) as a) myeloblastic, b) promyelocytic (APL), c) myelomonocytic (AMML), d) monoblastic (AMoL), e) erythroleukemia (AEL), or f) megakaryoblastic (AMegL). Occasional cases may seem to cross definition boundaries, other cases may be unclassifiable, and further cases may fall outside of each definition. Nonetheless, the four major types of leukemia (ALL, CLL, AML, and CML) account for the majority of leukemia cases.

Table 1. Classification of lymphoma/leukemia: Malignant neoplasms of the lymphatic and hematopoietic tissue (*6*).

Type	International Classification of Diseases
Lymphoma	
Non-Hodgkins	200
Reticulosarcoma	200.0
Lymphosarcoma	200.1
Hodgkins	201
Others and mixed (Hairy cell, histiocytosis)	202
Multiple myeloma (plasma cell origin)	203
Leukemia	
Lymphoid	204
Acute (ALL)	204.0
Chronic (CLL)	204.1
Myeloid	205
Acute (AML)	205.0
Chronic (CML)	205.1
Monocytic, etc.	206
Other	207
Unspecified	208

The four major classes of leukemias are generally regarded as distinct cancerous states. It would contradict our present understanding of cancer for a particular carcinogen to produce one type of leukemia in some people and another type in others, although it is not impossible to imagine this possibility. For example, a qualitative difference in metabolism could be demonstrated between two groups. In the case of benzene, no evidence exists of major differences in metabolism.

Association of Benzene and Leukemias

Clinical and epidemiological evidence consistently indicate that acute myeloid leukemia (AML) and its variants (alternatively called acute nonlymphocytic leukemias, or ANLL) can be caused by benzene exposure. While some studies have implicated other types of leukemia or even lymphomas, only AML and its variants have consistently been seen in excess in groups of workers with excess benzene exposure. Figures 1 through 6 show by type of leukemia the distribution of the cases associated with benzene exposure from modern published studies with five or more leukemia cases. In almost all, AML markedly predominates. Goldstein (*8*) reviewed the evidence on benzene-associated leukemia in 1977 and concluded that only AML and its variants had been definitely associated with benzene exposure; in every other type of leukemia, the evidence was not definite. Studies since that time have supported his conclusion.

Vigliani reported originally in 1964 (*9*) and again in 1976 (*3*) on the benzene and leukemia experience of Italian occupational medicine clinics (Fig. 1). Twenty-four of 24 cases of leukemia in benzene-exposed workers were AML. Aksoy reported originally in 1974 (*10*) and again in 1985 (*2*) on the experience of Turkish shoemakers and leatherworkers with benzene and leukemia (Fig. 2). Forty-three of 51 cases of leukemia were AML. The NIOSH study of the experience of Ohio Pliofilm rubber workers at two locations with benzene and leukemia (Fig. 3) was reported originally in 1977 by Infante et al. (*11*) and updated and extended in a 1987 report by Rinsky et al. (*5*). Six of 9 cases of leukemia were AML. The experience of a U.S. chemical company with benzene and leukemia (Fig. 4) was reported originally in 1978, by Ott et al. (*12*), and updated in a 1986 report by Bond et al. (*13*). Five of five cases of leukemia were AML. Recently, Yin (*4*) reported the experience of a Chinese industrial commune

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with benzene and leukemia (Fig. 5). Twenty of thirty cases of leukemia were AML. The only exception to the observation that two-thirds or more of leukemias associated with benzene are AMLs was the Wong et al. report (*14*). Wong studied workers occupationally exposed to benzene in U.S. chemical plants and reported no AML

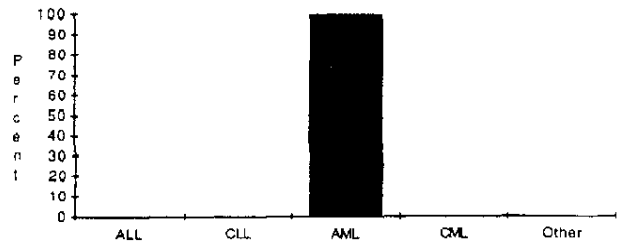

FIGURE 1. Percent distribution of Vigliani's benzene leukemia cases (n = 24) (*3*).

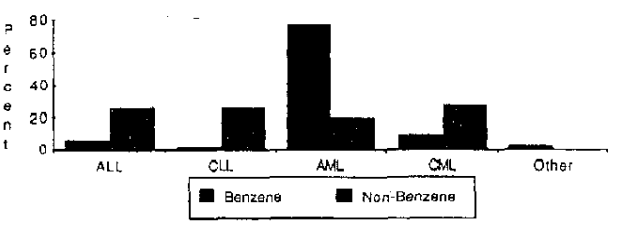

FIGURE 2. Percent distribution of Aksoy's benzene leukemia cases (n = 51) (*2*) and nonbenzene leukemia cases (n = 50) (*11*).

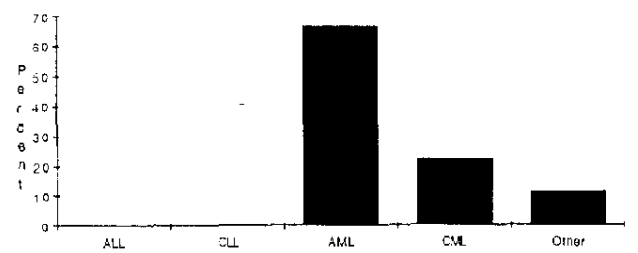

FIGURE 3. Percent distribution of Rinsky's benzene leukemia cases (n = 9) (*5*).

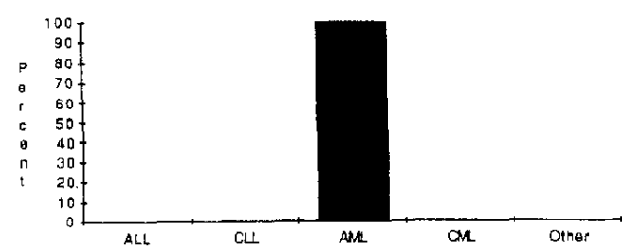

FIGURE 4. Percent distribution of Bond's benzene leukemia cases (n = 5) (*13*).

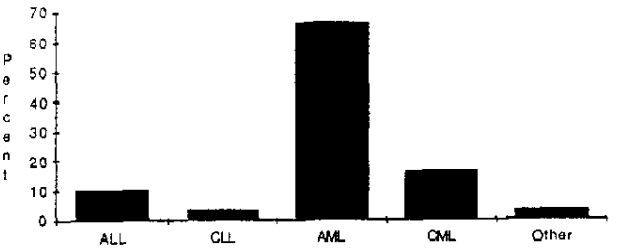

FIGURE 5. Percent distribution of Yin's benzene leukemia cases (n = 30) (*4*).

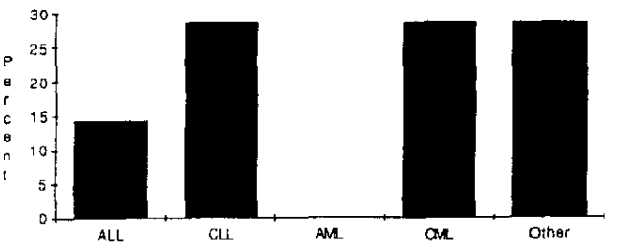

FIGURE 6. Percent distribution of Wong's benzene leukemia cases (n = 7) (*14*).

case among the seven leukemia cases observed (Fig. 6). Based on the experiences of other benzene-exposed groups, at least four cases of AML would have been expected among the seven leukemia cases. There are a number of other observations from the Wong et al. study where the results are different from other benzene studies. No case of leukemia was observed in their nonbenzene-exposed workforce.

Figure 3 presents the cell type distribution of leukemia cases in the most recent report of the NIOSH study of the Ohio Pliofilm rubber workers (*5*). Again, AML is the most common type. Six of the nine cases of leukemia reported in the study were AML. Five cases reported were myeloblastic and the sixth was AMoL. The pattern that again stands out is the dominance of AML among the leukemias of benzene-exposed workers.

There are few studies that provide comparative data on the proportion of leukemias expected to be AML in a nonbenzene-exposed worker population. Most population studies show that AML accounts for about one-third of all leukemias, typically ranging from 20 to 40%. The only direct comparison group is found in the study by Aksoy (*2*), which reported the leukemia types of 50 cases of leukemia in men seen in the same clinics but lacking known benzene exposure. He reported about equal numbers of each of the 4 types of cases (Fig. 2). Aksoy's studies of Turkish shoemakers were interesting because, while professor at the university hematology clinic in Istanbul, he was able to separate out 51 leukemia cases

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in workers with benzene exposure and 50 leukemia cases in persons without benzene exposure. For those cases that were benzene associated, AML prevailed (84%). For those not exposed to benzene, AML represented only 28% of the leukemia cases. For the nonbenzene-related background leukemias, Aksoy demonstrated a relatively equal representation of AML, ALL, CML, and CLL. AML is the only type that stood out in excess among the benzene-exposed cases compared to the nonbenzene-exposed cases (see Fig. 3). Thus, the studies of benzene workers, with 65 to 100% of their leukemia cases diagnosed as AML, quite likely represent an increased risk of AML.

The six studies described present a total of 126 leukemia cases among benzene exposed workers. The percentage distribution of these cases by type of leukemia is shown in Figure 7, along with expected percentiles based on 1978 US Leukemia Mortality data (*20,21*). There is little exposure information within these studies to group the workers into exposure categories other than the gross category of occupationally exposed to significant amounts of benzene, significantly great enough to be described in the literature as benzene exposed. Figure 7 reveals that when the cases from all six studies are viewed together, only AML stands out in marked excess above the others. This is the epidemiological basis for the conclusion that the acute myeloid leukemias are the only leukemias found in significant excess with significant benzene exposure. Thus, we propose that the distribution of AML among benzene exposed persons should serve as the basis of epidemiological and risk analysis.

We believe estimations of the risk of leukemia from benzene exposure should be based on the AML data, since this neoplastic disease alone has been shown to have an association with benzene exposure. It would be inappropriate to extrapolate the risk of AML to all leukemias when the risk appears to be biologically specific to AML. In studies where types of leukemia are not stated, analyses may provisionally have to be based on all leukemias, but specific diagnostic data should be obtained before the data are used in risk analysis. Some risk assessments have failed to compare the risks of the same disease between different studies.

Exposure definition and documentation have generally been the weakest aspect of risk assessment. Essentially, only AML is attributable to benzene exposure and other types of leukemia are not. The probability of benzene causing other leukemias is low, and may be zero. Some scientists disagree. They point to some studies where a nonsignificant excess of CML may be associated with benzene exposure, but they agree that this is not a consistent result. In order to believe that benzene causes CML, one must both explain the lack of consistency between and within studies, and reject the assumption that a given carcinogen produces the same cancer in all people.

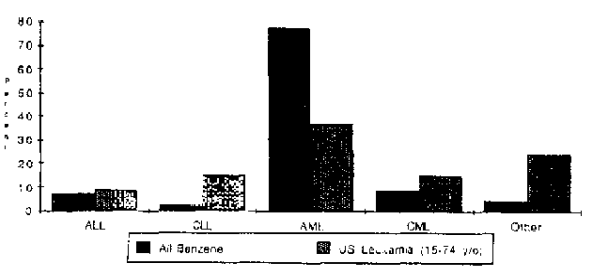

FIGURE 7. Percent distribution of benzene leukemia cases from six studies (n = 126) (*13,14*) and of U.S. leukemia deaths, ages 15–74, 1978 (*20,21*).

Risk Analysis of Benzene and Leukemia

The Ohio Pliofilm study (*11*) conducted initially by NIOSH through June 1975, reported the leukemia mortality of some groups of workers employed on the wet side of the benzene-using Pliofilm manufacturing process at three rubber plants in Ohio during the 1940s. Pliofilm was made using natural rubber, processing it by adding benzene to create rubber hydrochloride solution, and eventually spreading the resultant solution on a conveyor. The benzene was evaporated and recovered. A recent update of this study (*6*) extended the study group to include workers assigned to these areas at the three plants through 1965. The updated study reported the deaths from leukemia and lymphomas that occurred through 1981. Table 2 lists these leukemia and multiple myeloma cases as presented by the authors with the estimated cumulative benzene exposure calculations in part per million-years.

Plant History

Plant 1 at location 1 (St. Marys, OH) was established in 1939 and continued manufacturing Pliofilm until 1976. Plant 2A at location 2 (Akron, OH) commercially produced Pliofilm from 1936–1937 through 1949, and plant 2B, also at location 2, produced Pliofilm from 1949 until 1965. It is asserted that the exposures from Pliofilm process at each of the three plants were identical. With the exception of one report from plant 2B, all benzene exposure measurements came from plant 1. No exposure data are known for plant 2A. Since exposure data are only presented for the plant at location 1, the equivalency of exposure has to be accepted as a matter of faith.

Leukemia Mortality Analysis

Table 3 presents the same data as Table 2, but organized by plant location. These data are unusual. The two locations that are considered to be identical in terms of process and benzene exposure have distributions of cases that are entirely different with respect to the only type of leukemia (AML) consistently found in excess among benzene-exposed workers. All of the AML cases came from one location (plant 2A, where no benzene exposure data are available), while no cases of AML were diagnosed among the workers at plant 1 and 2B, where some benzene exposure data are available.

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All the cases of AML occurred in workers hired at plant 2A prior to 1945, a group observed for more than 37 years. Only one member of this group has died of AML since 1961. None of the workers hired into Plant 2A from 1945 to 1949 or into Plant 2B from 1949 to 1965 has been reported to have any type of leukemia in spite of 16 to 37 years of follow-up. None of the workers hired into plant 1 from 1939 to 1965 has been reported to have AML, although the follow-up period has ranged from 16 to 42 years. The relative risk of dying of AML during the first half of the period of observation was markedly greater than that of dying during the second half.

The cohort of people from plant 2A is incomplete. The personnel records from that location prior to 1945 are missing, and the only people whose records of employment exist prior to 1945 are those people who were hired prior to 1945 and continued working past 1945. It is noteworthy to observe that among the cohorts for whom employee rosters are complete (Akron 1945+ and St. Marys 1940+), there is no known case of AML. Thus, all AML cases appear to be in the employment prevalence cohort, and none appear to be in the employment incidence cohort. This would suggest that exposures prior to 1945 were critical.

Temporal Relationship

Latency is usually defined as the time interval from first exposure to date of death. The AML cases in this study reveal a range of 13.5 to 37 years since first exposure (Table 3) with a mean latency of 20.5 years. This is surprising, because AML secondary to other exposures is usually associated with latencies in the range of 0.5 to 10 years, with typical latencies of approximately 2 to 5 years (*17*). The latency range of AML after chemotherapy is generally 0.5 to 8 years and after radiotherapy is generally 4 to 10 years; therefore, the latency range is typically less than 10 years. The time of exposure to therapy is generally well known; the time of occupational exposure is more difficult to ascertain. The concept of latency with respect to occupational exposures uses the time of first exposure as a surrogate for the time of critical exposure. It may be that there are exposures subsequent to the initial exposure that are the inciting or critical exposures.

The latencies reported in the Rinsky et al. study (*5*) also have long duration in comparison to data from other benzene-exposed groups. Unlike the Rinsky study (*5*), which shows a mean latency of 20.5 years, the data of Yin

Table 2. Case list of leukemias and multiple myelomas (*11*).

Case	Location	Diagnosis[a]	Latency, years	Year of death	Cumulative benzene exposure, ppm-year
1	1	MoL	17	1958	49.99
2	1	CML	2	1950	0.10
3	2	AML	13.5	1958	259.5
4	2	AML	15.5	1960	498.23
5	2	AML	22	1961	478.45
6	2	AML	20	1961	639.84
7	2	AMoL	15	1957	98.55
8	1	ML	3.5	1954	10.16
9	2	AML	37	1979	252.66
10	1	MM	25.5	1980	19.5
11	1	MM	22.5	1963	0.11
12	1	PCS	24.5	1968	652.66
13	1	MM	26.5	1981	7.75

[a]MoL, monocytic leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; AMoL, acute monoblastic leukemia; ML, myeloid leukemia; MM, multiple myeloma; PCS, plasma cell sarcoma.

Table 3. Case list of leukemias and multiple myelomas ordered by location and by year of hire (*11*).

Location	Diagnosis[a]	Year of hire	Latency, years	Year of death	Cumulative benzene exposure, ppm-year
2	AML	1939	22	1961	478.45
2	AML	1941	20	1961	639.84
2	AMoL	1942	15	1957	98.55
2	AML	1942	37	1979	252.66
2	AML	1944	13.5	1958	259.5
2	AML	1944	15.5	1960	498.23
1	MM	1940	22.5	1963	0.11
1	MoL	1941	17	1958	49.99
1	PCS	1943	24.5	1968	652.66
1	CML	1948	2	1950	0.1
1	ML	1950	3.5	1954	10.16
1	MM	1954	25.5	1980	19.5
1	MM	1954	26.5	1981	7.75

[a]AML, acute myeloid leukemia; AMoL, acute monoblastic leukemia; MM, multiple myeloma; MoL, monocytic leukemia; PCS, plasma cell sarcoma; CML, chronic myeloid leukemia; ML, myeloid leukemia.

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(4) have an average latency of 11 years. Further, the data of Aksoy (2) have an average latency of 9 years. Thus, the NIOSH data are also unusual with respect to AML latency in comparison to other studies of benzene-associated leukemias.

The temporal relationship between exposure and disease may also be examined on the basis of the time interval between the date of last exposure and the date of death or diagnosis. An analysis of the literature in 1980 showed that 80% of benzene-associated leukemia deaths occurred no more than two years after their last benzene exposure (18). The implication of these results is that the risk of leukemia decreases with time after exposure, which suggests that benzene may act at a later stage in the carcinogenic process, perhaps through action on promotion or disease progression.

The idea that benzene is not an initiator is consistent with two other facts: benzene has not caused mutagenic effects at the level of base-pair changes (transitions, short deletions, frame shifts, and so forth) in appropriate short-term tests, and benzene pancytopenia frequently precedes leukemia. The Chinese study (4) reported a leukemia risk ratio of 1500 for benzene-exposed workers with pancytopenia in comparison with a leukemia risk ratio of 5 to 10 for the total benzene-exposed work force. This observation suggests that pancytopenia may be a necessary precursor or threshold condition in order for benzene-induced leukemia to develop subsequently.

Benzene Exposure Assumptions

Rinsky et al. (5) estimated the AML cases at location 2 (plant 2A) to have cumulative benzene doses generally of 250 to 650 ppm-years with a median exposure estimate of 370 ppm-years. Unlike the non-AML cases, none of the AML cases had low cumulative benzene exposures. The non-AML cases had a median exposure estimate of 10 ppm-years. There does not seem to be a gradual increase in frequency by dose, with some of the cases occurring at lower doses and more at higher doses. Furthermore, since there are no known industrial hygiene data for any plant prior to 1949, all of the benzene exposures assigned to the leukemia cases at location 2 are based on industrial hygiene data from location 1 and from data collected in subsequent decades. As the authors state, "Benzene exposure levels measured at location 1 were assumed to be identical to exposure levels in corresponding areas at location 2, when actual exposure measurements did not exist" (5).

In Rinsky's exposure analysis, historical air sampling data were used where available, and estimates based on existing data were used when no data were available. The industrial hygiene data referenced (5) were collected in the 1950s, 60s, and 70s, and then extrapolated back in order to estimate exposures in the 1940s. Most of the samples were area samples of unspecified duration, and only the data from the mid-1970s were 8-hr time-weighted averages. Nonetheless, all the data appear to have been used as 8-hr, time-weighted average personal exposure measurements.

Most of the benzene exposures estimated for workers in Pliofilm production occurred during the 1940s, when minimal or no exposure data were collected. The estimation of cumulative benzene exposures for specific individuals is limited to the time they spent in Pliofilm production and is markedly dependent upon the assumptions used to develop their exposure estimates for the 1940s. The work forces at the two plants differed in their potential for exposure to benzene and other chemicals at non-Pliofilm job sites. Plants 2A and 2B were part of a large industrial tire-building complex, and plant 1 was isolated in a small town in southern Ohio. Furthermore, the assumptions made regarding exposure levels in the Pliofilm operations in the 1940s are in dispute.

Rinsky et al. (5) assumed that for a given job the exposure levels were constant backward over time unless specific data indicated otherwise. In other words, the exposure levels were assumed to be the same both during the periods for which exposure data existed and during prior periods for which no data existed. Thus, if the only data for a specific job produced an estimate of 15 ppm when measured in 1976, they assumed that exposure in that job in 1945 was also 15 ppm. While this procedure might appear to be reasonable as a first approximation in a retrospective study, alternatives exist to the assumption that exposure levels did not change. Other alternatives might include the assumption that the exposure level continued at a certain measured level until observed to be lower, or that the decrease (or increase) in level progressed uniformly from one period of measurement to another.

Crump and Allen (19) developed an alternative exposure assumption in an analysis of the industrial hygiene data in a report for OSHA. Crump and Allen estimated both a cumulative benzene exposure amount and a maximum or peak intensity benzene exposure level for each of the employees in Pliofilm production. To calculate or estimate exposure levels for jobs during time periods for which no data existed, they calculated all exposure data for a particular job as a percentage of the allowable level at that time and then applied that percentage (or proportion) to each time period. Thus, if the data in 1976 indicated that the average exposure to benzene in a particular department was 15 ppm, i.e., 1.5 times the 10 ppm standard in effect in 1976 (15 ppm = 1.5 × 10 ppm), then the benzene exposure in that same department in 1945 was assumed to be 1.5 times the 100 ppm standard in effect in 1945 (i.e., 1.5 × 100 ppm = 150 ppm). It is important to remember that the benzene exposure standard dropped from a maximum allowable concentration (MAC) of 100 ppm in 1940 to a level of 50 ppm (8-hr time-weighted average, TWA) in 1947, to a level of 35 ppm (8-hr TWA) in 1948, to 25 ppm in 1957, and in 1969 to 10 ppm. In 1987, the standard (20) was lowered to 1 ppm, based to a considerable extent on the NIOSH report. As the Crump and Allen exposures were related to the standards of the time, the benzene exposure estimates for the early years were much greater in the Crump and Allen analysis than in the Rinsky analysis.

An additional difference in the assumptions of Rinsky

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et al. (5) and of Crump and Allen (19) is that the NIOSH group limited their exposure calculations to Pliofilm workers who worked on the wet side of the process (the wet side was the area in the 1940s where benzene was considered to be perceptible in the air), whereas the Crump and Allen analysis reported on exposure calculations for all identified Pliofilm workers, whether assigned to the wet side or to the dry side.

The determination of which set of exposure assumptions provides the more valid basis for calculating the risk cannot be based on information in these reports alone. Neither Rinsky et al. (5) nor Crump and Allen (19) provide independent data that permit determining which of the two assessments most likely represents the actual benzene exposures. The reports by Kipen et al. (21,22) analyzing hematology studies of the workers at plant 1 does provide some insight.

Because benzene causes hematotoxicity as demonstrated by reduced blood cell counts, complete blood cell counts were frequently conducted on Pliofilm workers. The hematology data from plant 1 were analyzed by Kipen, Cody, and Goldstein (22), who identified the blood counts of individual workers, determined from their work histories their job assignments at the time the blood specimens were taken, and specified the benzene exposure level that either Crump and Allen (19) or Rinsky et al. (5) would have assigned them for that job at that time. Analysis showed a correlation coefficient for the white blood cell counts of 0.72 with the Crump and Allen exposure estimates for the years 1940 to 1948 and a correlation coefficient of 0.03 with the Rinsky et al. exposure estimates for the same time period. Thus, with respect to hematotoxicity, the exposure estimates of Crump and Allen better reflect the hematological status of Pliofilm workers during the 1940s. We believe it is reasonable to assume that exposure estimates that correlate best with the evidence of hematotoxicity in the same cohort would provide the most reliable exposure estimates to use in a quantitative risk analysis, particularly if benzene-related leukemia is found to develop from a precursor condition of benzene-related hematotoxicity.

Quantitative Risk Analysis

For developing a quantitative risk assessment for benzene based on the mortality data of the Ohio Pliofilm study (5), dispute exists over which worker population, which exposure estimates, and which leukemias should be used.

The NIOSH study by Rinsky et al. (5) limited the population to the Pliofilm workers who worked in the wet side section through 1965. Crump and Allen (19) used as their study population all known workers in the Pliofilm operation through 1965, including both the workers from the wet side and the workers from the dry side of the Pliofilm operation. We concur with Crump and Allen that for a quantitative risk analysis the studied cohort should include all those in Pliofilm manufacture, and not just those from the wet side. Inclusion of as full a spectrum of exposure as feasible increases the robustness and reduces the uncertainty in applications of the derived risk estimate. Exclusion of the dry side workers specifically diminishes the low end of the exposure spectrum.

Rinsky et al. assumed, in the absence of exposure data, that exposure over time was constant on an absolute scale; Crump and Allen assumed, in the absence of exposure data, that exposure over time was constant on a relative scale, relative to the occupational benzene standard of the time. Rinsky et al. concentrated on the cumulative benzene exposure; Crump and Allen explored the interpretation of both the cumulative benzene exposure estimates and the peak benzene exposure estimates. We would have explored a number of different exposure assumptions, as indicated, and for both peak and cumulative exposures. With respect to exposure data, we would have given preference to the Crump and Allen assumptions, based on the analysis by Kipen et al. (21) of the hematology data at plant 1.

Both assessments used the exposure data from location 1 to serve as a surrogate measure of exposure at location 2. If the benzene exposure is thought to be the critical determinant of risk, we find it difficult to accept that the benzene exposure levels at location 2, where all of the AML cases occurred, could have been the same as the exposure levels at location 1, where no AML cases occurred. We would have reported the risk analysis of each location separately.

Both Rinsky et al. and Crump and Allen incorporated all leukemias in their analyses. We would have reported separately the analysis of risk of acute myeloid leukemia (AML). Based on the observations in the larger studies of leukemia in benzene-exposed workers, we believe that evaluation of the risk of benzene-associated leukemia should specifically target upon AML. The calculated risk values would thus become more significant, both statistically and biologically.

The most appropriate study population would have consisted of all persons who ever worked in the Pliofilm operation. Unfortunately, the personnel records no longer exist for persons who worked in the Pliofilm operation in plant 2A and terminated their Pliofilm assignment prior to 1945. Therefore, those individuals cannot be included in the study population. In view of this exclusion, the population is best analyzed as a combination of a cross-sectional study cohort and an employment incidence cohort. We would have separately analyzed the risks for the employment incidence cohort from that of the cross-sectional cohort and have discussed the differences in observations.

Separating the analysis into multiple strata is a problem when only a few cases (6 AML, 2 CML, and 1 MoL) of leukemia have been observed. Nonetheless, it is important to observe whether the cases (and the risks) do concentrate within the most rigorously defined cohort or in its periphery.

Graphical Risk Analysis

Figure 8 serves as an example of an analytic model exhibiting the exposure circumstances necessary for the de-

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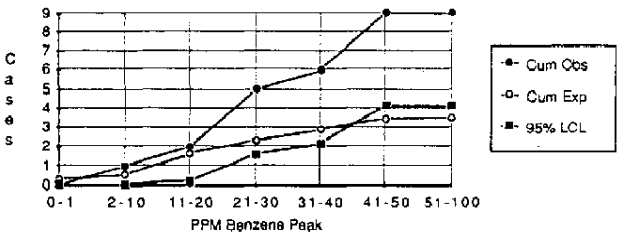

FIGURE 8. Benzene-leukemia dose relationship by peak benzene level (ppm) of Rinsky (*5*) for all known 1940–1965 Pliofilm workers.

velopment of a significant excess risk of disease mortality. As a model, the cumulative leukemia risk (using all 9 leukemia cases) with benzene exposure expressed by peak exposure experienced by workers is presented for sequentially higher peak levels of benzene exposure. This particular graph shows peak benzene exposure levels according to Rinsky's (*5*) exposure assumptions. The cohort is defined according to Crump and Allen's (*19*) criteria. The three lines represent sequentially the cumulative number of cases of leukemia observed, the cumulative number of cases of leukemia expected, and the 95% lower confidence limit of the observed number of leukemia cases. A statistically significant excess of leukemia cases has been observed when the 95% lower confidence limit is greater than the cumulative expected. It is not until the last two exposure levels are included that there is a significant excess of leukemia observed among the benzene exposed workers. Thus, if the NIOSH assumptions of Rinsky (*5*) are used, this occurs at a peak benzene level greater than 40 ppm (Fig. 8). If the exposure assumptions of Crump and Allen (*19*) are used, a statistically significant excess of leukemia cases is observed only when workers with exposures above 250 ppm are included (Fig. 9).

Risk analysis for all leukemia classes based on both the exposure estimates and the cohort assumptions of Rinsky (*5*) would lead to the conclusion that a significant excess risk of leukemia was not observed until the study population included those with a peak benzene exposure of greater than 20 ppm or an estimated cumulative benzene exposure of greater than 250 ppm-years (Table 4). Similar analyses based on the exposure estimates of Crump and Allen (*19*) and applied to all the studied workers at

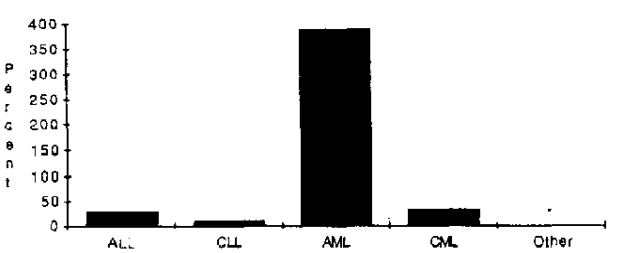

FIGURE 9. Percent observed/percent expected by type of leukemia for all six studies (*2–4,6,13,14*).

Table 4. Benzene exposure characteristics of excess leukemia risk based on different assumptions of study cohort and of exposure parameters.

	Study parameters		Significant risk excess	
Author	Cohort	Exposure	Peak	Cumulative
Rinksy (*5*)	Wet side	Linear	> 20 ppm	> 250 ppm-year
	Total	Linear	> 40 ppm	> 250 ppm-year
	Wet side	Proportional	> 250 ppm	> 250 ppm-year
Crump (*19*)	Total	Proportional	> 250 ppm	> 450 ppm-year

the plants lead to the conclusion that a significant excess risk of leukemia was not observed for those in the study group who had an estimated peak benzene exposure of less than 250 ppm or an estimated cumulative benzene exposure of less than 450 ppm-years (Table 4). Assuming that these exposures occurred over a 40-year worklife, the Rinsky assumptions using this model would reach the conclusion that a statistically significant leukemia risk existed with peak benzene exposure over 20 ppm and a worklife average exposure over 6 ppm (250 ppm-yrs/40 years = 6.25 ppm). Similarly, the Crump assumptions using the same model would conclude that a statistically significant leukemia risk existed with peak benzene exposure over 250 ppm and a worklife average exposure over 11 ppm (450 ppm-yr/40 years = 11.25 ppm). Thus, the determination as to whether the previous benzene standard of 10 ppm included a significant leukemia risk is markedly dependent upon the methodological assumptions made in analyzing the data.

Conclusions

Available data strongly support the conclusion that AML can be caused by excessive benzene exposure. This is a consistent observation among all recent studies with the exception of that of Wong (*14*).

There is no consistent evidence for production of ALL, CML, or CLL by benzene exposure. A belief that benzene causes CML would necessitate the proposition that the same exposure causes different tumors in different groups of people.

An examination of the two parts of the Pliofilm cohort suggests a difference between the two plants in that AML cases occurred at only one plant (2A) and only among those already working in the plant prior to 1945. One explanation consistent with the data is that the men working in plant 2A prior to 1945 had a much higher lifetime benzene exposure than previously assumed and more than those men working in plant 2A or 2B after 1945.

The overall data seem more consistent with the dose assumptions of Crump and Allen than those of Rinsky et al. The exposure estimates derived from the Crump and Allen assumptions correlate very well with the hemotoxicity data from plant 1; the exposure estimates derived from the Rinsky et al. assumptions do not. Therefore, the

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Crump and Allen estimates are more likely to provide a better representation of workers' exposures.

The Rinsky et al. study shows a strong nonlinearity with dose using either the Rinsky et al. (*5*) or the Crump and Allen (*19*) exposure estimates. Furthermore, the risk ratio does not appear to stay constant after a latent period, but appears to fall with time.

The nonlinearity of risk with exposure dose, the observation of pancytopenia prior to leukemia, and the latent period are all consistent with leukemia as an indirect effect of benzene.

If the data are to be used for quantitative assessment, the analysis should be limited to AML cases, the surrogate nature of the exposure data should be noted, and the observation that the excess cases of AML all have attributed cumulative benzene exposures of 250 to 650 ppm-years should be prominently observed.

We propose that future assessments of leukemic risk from benzene exposure be based on the distribution pattern of AML alone, as that is the sentinel neoplastic disease associated with excess benzene exposure. This concept is consistent with the assessment of Goldstein (*8*) and with the studies of Vigliani (*3*), Aksoy (*2*), Rinsky (*5*), Bond (*13*), and Yin (*4*).

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